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Medication adherence across oral and injectable disease-modifying therapies in multiple sclerosis: A retrospective single-center real-world study

Abstract

Background: Adherence to Disease-Modifying Therapy (DMT) is essential to obtain the intended benefits of long-term Multiple Sclerosis (MS) treatment. We evaluated adherence to self-administered DMTs and explored its association with route of administration, individual medication, and patient characteristics. **Methods:** We conducted a retrospective single-center observational study of adults with MS receiving self-administered DMTs through the hospital pharmacy of a tertiary Spanish hospital during 2021. Adherence over 12 months was assessed from dispensing records using the Medication Possession Ratio (MPR); MPR ≥0.80 defined adherence. Demographic, clinical, and pharmacological variables were examined using bivariate analyses and exploratory logistic regression. **Results:** The source cohort comprised 214 patients; 62.1% were women and 95.3% had relapsing-remitting MS. Adherence data were evaluable for 209 patients [verify denominator against source database], of whom 190 (90.9%) were adherent. Adherence was higher for oral than injectable DMTs (95.1% vs 84.9%; p=0.011). It ranged from 77.4% with subcutaneous interferon beta-1b to 97.6% with dimethyl fumarate, with an overall unadjusted association between drug and adherence (p=0.047). No clear associations were observed for the evaluated demographic or clinical characteristics. In exploratory adjusted analysis, the global medication effect was not statistically significant (p=0.098). **Conclusion:** Adherence to self-administered DMTs was high in this real-world cohort. Oral therapies and some individual regimens showed more favorable unadjusted adherence patterns than older injectable therapies, but the limited number of non-adherence events warrants cautious interpretation. Regimen-specific pharmacy follow-up may help identify patients requiring additional adherence support.

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Keywords: Multiple sclerosis; Medication adherence; Disease-modifying therapy; Medication possession ratio; Oral therapy; Hospital pharmacy.

Introduction

Multiple Sclerosis (MS) is a chronic immune-mediated disease of the central nervous system for which long-term Disease-Modifying Therapies (DMTs) are used to reduce inflammatory disease activity and modify its clinical course. The expanding therapeutic landscape has created substantial variation in route of administration, dosing frequency, tolerability, monitoring requirements, and treatment burden. Recent clinical work published in the Journal of Neurology and Neurological Sciences also reflects continued interest in pharmacological treatment strategies in Relapsing-Remitting MS (RRMS) [1].

Obtaining the intended benefit of a long-term DMT depends not only on selecting an appropriate therapy but also on whether patients can sustain the prescribed treatment. Real-world studies have reported substantial variability in adherence and persistence among people with MS [2-9]. In a population-based

Canadian study, treatment discontinuation and incomplete adherence remained relevant problems across DMTs, while a large US analysis of patients newly initiating self-injectable or oral therapy showed that oral administration alone did not guarantee better adherence [2,3]. In a prospective Canadian study of injectable DMTs, non-adherence was associated with factors such as cognitive difficulties, demonstrating that patient-level barriers can be as important as regimen characteristics [4].

Evidence regarding administration route is heterogeneous. In a Spanish study, Morillo Verdugo et al. reported an overall adherence rate of approximately 71%, with no statistically conclusive oral-versus-injectable difference using their adherence assessment [5]. In contrast, Zanga et al. found oral administration associated with greater adherence in multivariable analysis, and Finnish registry data showed particularly high adherence for oral teriflunomide and dimethyl fumarate compared with several older injectable DMTs [8,9]. Medication beliefs, socioeconomic circumstances, cognitive status, disability, adverse effects, treatment complexity, and regimen convenience have all been implicated in adherence behavior [4,6-8].

Hospital-pharmacy dispensing data provide an objective and routinely available means of estimating whether patients possess sufficient medication to follow treatment. The Medication Possession Ratio (MPR) is commonly used in retrospective adherence research, although possession cannot establish whether a medicine was actually taken or injected correctly [3,10]. A commonly used operational threshold defines patients with an MPR of at least 0.80 as adherent [3,8-10].

The primary objective of this study was therefore to determine 12-month adherence to self-administered DMTs among patients with MS receiving their medication from a tertiary hospital pharmacy in Spain. The secondary objective was to examine whether adherence differed according to demographic and clinical characteristics and, particularly, according to individual DMT and route of administration. Based on prior literature and the study protocol, we hypothesized that overall adherence would be high and that adherence to oral treatment would exceed adherence to traditional injectable therapies.

Materials and methods

Study design and setting: We performed a retrospective, observational, single-center study at Hospital Clínico Universitario Lozano Blesa, a tertiary hospital serving Health Area III of Aragón, Spain. The study population comprised adults with MS receiving an active self-administered DMT and obtaining medication from the hospital outpatient pharmacy during 2025.

Participants: Eligible patients were aged ≥18 years, had an MS diagnosis established according to the applicable 2010 McDonald criteria or the 2017 revision, and were receiving one of the self-administered DMTs evaluated in the study. Patients without sufficient follow-up or data were excluded. The treatment set was: Subcutaneous interferon beta-1b, intramuscular interferon beta-1a, subcutaneous interferon beta-1a, glatiramer acetate, fingolimod, teriflunomide, and dimethyl fumarate.

Intravenous DMTs were not evaluated because the study focused on medication collected from the pharmacy for subsequent self-administration at home. Cladribine was excluded because of its distinctive intermittent dosing schedule, and Siponimod was not included because of its recent introduction at the time of data collection.

Variables and data sources: Demographic variables included sex, age at treatment initiation, and age at MS diagnosis. Clinical variables included MS phenotype, disease duration, Expanded Disability Status Scale (EDSS) score, previous relapses, previous hospitalizations, and recorded comorbidities or MS-related symptoms. Pharmacological variables included DMT, route of administration, treatment line, duration of current therapy, polypharmacy (defined in the source protocol as >5 medications per day), and documented adverse effects. Data were obtained from the Dominion® Farm tools® outpatient-dispensing system and the electronic health record.

Adherence assessment: Adherence was evaluated during a 12 month period using MPR derived from pharmacy dispensing records. The study protocol defines MPR as the number of days for which medication was available from dispensing records divided by the number of days for which medication should have been available according to the prescribed regimen. An MPR ≥0.80 was classified as good adherence.

Ethics

The study was approved by the Research Ethics Committee of Aragón (CEICA; EPA22/022; 3 May 2026). Patient information was processed in accordance with applicable European and Spanish data-protection requirements.

Results

Study population: A total of 214 patients were included in the descriptive cohort. Women comprised 62.1% (n=133). Median age at treatment initiation was 44 years (range, 18-66), and median age at diagnosis was 32 years (range, 7-55). RRMS was present in 204 patients (95.3%), while 10 (4.7%) had secondary progressive MS (SPMS); no patient had primary progressive MS. Median disease duration was 11 years (range, 0.2-45), and median EDSS score was 1.5 (range, 0-8).

At least one previous relapse was reported for 110 patients (51.4%). There was a median of two previous relapses (range, 0-17). Eighty-four patients (39.3%) had experienced at least one previous hospitalization.

Comorbidities or MS-associated symptoms were recorded in 70.9% of the patients. Mental-health disorders was the most frequent category (64.5%), followed by anxiety (50.5%), depression (36.4%), sleep disorders (25.2%), migraine/headache (23.4%), metabolic disease and gait disorder (21.5% each), and memory impairment (19.6%).

Treatment characteristics: In the full cohort, 127 patients (59.3%) were receiving an oral DMT and 87 (40.7%) an injectable DMT. Teriflunomide was the most frequently prescribed agent (26.6%; n=57), followed by dimethyl fumarate (20.6%; n=44), subcutaneous interferon beta-1b (14.5%; n=31), glatiramer acetate (12.6%; n=27), fingolimod (12.1%; n=26), intramuscular interferon beta-1a (7.0%; n=15), and subcutaneous interferon beta-1a (6.5%; n=14). Median treatment line was 2 (range, 1-5), median duration of the current DMT was 63.8 months (range, 1.2-300.9), 82 patients (38.3%) met the study definition of polypharmacy, and 115 (53.7%) had a documented treatment-related adverse effect.

Adherence: Among 209 evaluable patients (5 were excluded due to lack of information), 73 of 86 receiving injectable DMTs were adherent (84.9%), compared with 117 of 123 receiving oral DMTs (95.1%).

Table 1: Adherence according to route and individual DMT.

Treatment group	Evaluable (n)	Adherent (n)	Adherence, %
All evaluable patients	209	190	90.9
Injectable DMT	86	73	84.9
Oral DMT	123	117	95.1
Interferon beta-1b, SC	31	24	77.4
Interferon beta-1a, IM	14	11	78.6
Fingolimod	26	24	92.3
Glatiramer acetate	27	25	92.6
Interferon beta-1a, SC	14	13	92.9
Teriflunomide	56	53	94.6
Dimethyl fumarate	41	40	97.6

Route of administration was associated with adherence (p=0.011; Phi/Cramer's V=0.175). The analysis reported Yule's Q=0.55 for the relationship between oral treatment and good adherence.

Adherence also differed across individual DMTs in the unadjusted analysis (p=0.047; Cramer's V=0.247). The lowest adherence proportions were observed with subcutaneous interferon beta-1b (24/31; 77.4%) and intramuscular interferon beta-1a (11/14; 78.6%). Adherence was 24/26 (92.3%) for fingolimod, 25/27 (92.6%) for glatiramer acetate, 13/14 (92.9%) for subcutaneous interferon beta-1a, 53/56 (94.6%) for teriflunomide and 40/41 (97.6%) for dimethyl fumarate. The adjusted standardized residual for non-adherence with subcutaneous interferon beta-1b was 2.8, identifying that category as the principal contributor to the unadjusted drug-by-adherence association.

No statistically significant bivariate associations were reported for sex (p=0.893), age at treatment initiation (p=0.858), age at diagnosis (p=0.053), MS phenotype (p=1.000), disease duration (p=0.254), EDSS (p=0.348), previous relapse status (p=0.205), number of previous relapses (p=0.391), previous hospitalization status (p=0.097), number of hospitalizations (p=0.187), treatment line (p=0.761), DMT duration (p=0.530), polypharmacy (p=0.193), or adverse effects (p=0.313). The source report also found no statistically significant association with the individual comorbidity categories assessed.

Exploratory multivariable analysis: In the logistic regression, the global medication term did not reach statistical significance (Wald=10.717; p=0.098). Using dimethyl fumarate as the reference category, lower odds of adherence were reported for intramuscular interferon beta-1a (OR 0.084; 95% CI 0.008-0.920; p=0.043) and subcutaneous interferon beta-1b (OR 0.077; 95% CI 0.009-0.687; p=0.022). The remaining drug contrasts were not statistically significant, nor were sex or age. Nierkerk R^2 was 0.119, and the Hosmer-Leeshawn test gave p=0.610.

Table 2: Exploratory multivariable logistic regression for adherence.

Variable	OR	95% CI	p
Medication, global effect	-	-	0.098
Interferon beta-1a IM vs dimethyl fumarate	0.084	0.008–0.920	0.043
Interferon beta-1b SC vs dimethyl fumarate	0.077	0.009–0.687	0.022
Glatiramer acetate vs dimethyl fumarate	0.288	0.024–3.421	0.325
Interferon beta-1a SC vs dimethyl fumarate	0.294	0.017-5.166	0.403
Fingolimod vs dimethyl fumarate	0.298	0.026-3.483	0.335
Teriflunomide vs dimethyl fumarate	0.419	0.042-4.215	0.460
Sex	0.844	0.300-2.376	0.748
Age	1.014	0.962–1.069	0.599

Discussion

In this retrospective hospital-pharmacy cohort, adherence to self-administered MS DMTs was high: 90.9% of patients with apparently evaluable MPR data met the prespecified threshold of 0.80. Oral DMTs had higher unadjusted adherence than traditional injectable therapies, and adherence varied across individual medications, with subcutaneous interferon beta-1b showing the lowest proportion and dimethyl fumarate the highest. By contrast, none of the demographic, disease-related, comorbidity, treatment-duration, polypharmacy or adverse-effect variables examined showed a statistically significant bivariate association with adherence.

The overall adherence proportion is higher than that reported in several previous MS cohorts, although direct comparison is difficult because definitions, treatment eras, populations and adherence instruments differ markedly. For example, Morillo Verdugo et al. reported approximately 71% adherence in a Spanish multicenter setting using a questionnaire-based approach, whereas Zanga et al. observed substantially lower MPR-defined adherence in another real-world cohort [5,8]. These discrepancies illustrate why an adherence percentage should not be interpreted independently of its measurement method. Pharmacy-dispensing measures quantify medication availability and avoid recall bias, but they can overestimate actual medication-taking behavior because collection of medication does not prove ingestion, injection, correct technique or dosing at the prescribed time.

The favorable adherence observed for oral treatment in our cohort is consistent with some, but not all, previous research. Zanga et al. reported a significant association between oral administration and greater adherence, while a Finnish population analysis found adherence of 91.7% with teriflunomide and 86.9% with dimethyl fumarate, compared with lower levels for beta-interferons and glatiramer acetate [8,9]. A Spanish investigation specifically examining administration route likewise addressed the possibility that route may influence adherence behavior [11].

Other studies have produced different findings. In a large US claims analysis of patients newly initiating oral or self-injectable DMTs, Munsell et al. found similar proportions achieving MPR ≥0.80 and no independent route effect after adjustment [3]. Morillo Verdugo et al. also did not demonstrate a statistically significant superiority of oral therapy in their Spanish cohort [5]. Route should therefore be viewed as one marker of regimen burden rather than a universally causal determinant. Dosing frequency, adverse-effect profile, injection-related inconvenience, individual preference, treatment beliefs, previous therapeutic experience and the intensity of pharmaceutical or nursing support may all modify the relationship.

The individual-drug results reinforce this interpretation. Subcutaneous interferon beta-1b, administered every other day in the treatment regimen represented in this cohort, had an adherence proportion of 77.4%, whereas once-daily teriflunomide and oral dimethyl fumarate had adherence proportions of 94.6% and 97.6%, respectively. However, route and medication are inseparable in the present treatment set, and each medication

also differs in dosing frequency, treatment indication, tolerability, time on market and patient selection. The observed association therefore cannot determine whether oral administration itself, lower administration burden, other drug-specific characteristics or confounding by treatment selection explains the difference.

The particularly high dimethyl fumarate adherence in this cohort should also not be treated as an intrinsic characteristic of the molecule. Other real-world datasets have reported substantially lower adherence to dimethyl fumarate than observed here, demonstrating important health-system and cohort effects. Real-world studies of oral DMT persistence and adherence have shown that relative rankings between agents can change according to population, follow-up period and analytic definition. The appropriate conclusion is therefore that dimethyl fumarate had the highest observed adherence in this hospital cohort, not that it universally produces the best adherence.

The absence of significant associations with age, sex or measured clinical characteristics is broadly compatible with studies in which medication beliefs or behavioral factors were stronger determinants than routine demographic measures. Neter et al., for example, found that beliefs about medication predicted later adherence in a prospective MS cohort [7]. Nevertheless, other studies have identified age, sex, depression, socioeconomic conditions, cognitive problems or disability as relevant determinants [3,4,6]. The present null findings should therefore not be interpreted as evidence that such patient-level characteristics never affect adherence. Socioeconomic status, educational level, family support and treatment beliefs were not available in the electronic record and were explicitly acknowledged as missing variables in the original study.

The current therapeutic environment further limits the generalizability of a route-based comparison conducted in 2021. Newer self-administered regimens can have very different dosing frequencies and support structures from traditional interferons. Recent real-world evidence involving monthly subcutaneous ofatumumab, for example, shows that an injectable regimen can achieve adherence/persistence comparable with or more favorable than several alternative DMTs. Thus, the clinically meaningful construct may increasingly be overall regimen burden and patient-treatment fit, rather than route alone.

This study has several strengths. It links clinical information with objective hospital-pharmacy dispensing records, evaluates seven commonly used self-administered DMTs within a single healthcare system, uses a 12-month adherence window, and provides agent-specific as well as route-specific results. These features make the study relevant to hospital pharmacists, neurologists and multidisciplinary MS teams because patients at greatest risk of refill gaps can potentially be identified from routinely available dispensing information.

Several limitations require explicit emphasis. First, this was a retrospective single-center study, limiting external generalizability. Also, MPR measures possession rather than actual administration and may consequently overestimate true adherence. Finally, only 19 non-adherence outcomes occurred, making the multivariable model vulnerable to sparse-data bias and overfitting.

Conclusion

Adherence to self-administered DMTs was high among patients with evaluable dispensing data in this single-center real-world MS cohort. Oral DMTs were associated with higher unadjusted adherence than traditional injectable DMTs, and adherence varied among individual medications, with the lowest observed proportion for subcutaneous interferon beta-1b. However, the adjusted evidence for an independent medication effect was uncertain, and the small number of non-adherence events precludes strong causal or predictive conclusions. Hospital-pharmacy dispensing records may nevertheless be useful for identifying treatment-specific adherence gaps and targeting individualized pharmaceutical care. Future multicenter studies should integrate refill data with patient-reported adherence, treatment beliefs, socioeconomic factors and contemporary DMT regimens.

Declarations

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Conflicts of interest: The authors declare no conflicts of interest.

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